

## Supravalvar aortic stenosis

E. C. Martin and I. F. Moseley

From St. Bartholomew's Hospital, London

*Twelve cases are described and 200 published cases analysed. The supravalvar aortic stenosis syndrome is one manifestation of the idiopathic hypercalcaemia of infancy syndrome, and the possible aetiologies are discussed. Another presentation of supravalvar aortic stenosis is in the so-called familial form, but there may exist considerable confusion between these two forms, as less than 50 per cent of those without physical stigmata have a positive family history, and the severe form of the idiopathic hypercalcaemia of infancy syndrome presenting with supravalvar aortic stenosis may have intermediate, or even normal facies. Management depends largely on the severity of the outflow tract obstruction. Full classification may be delayed until the aetiology is completely understood.*

In 1958, Denie and Verheugt diagnosed supravalvar aortic stenosis by retrograde arterial catheterization of the left ventricle, and on reviewing the published reports, found 11 other cases mentioned, of whom 3 had mental retardation. Three years later in 1961, Williams, Barratt-Boyes, and Lowe described 4 cases of supravalvar aortic stenosis with the triad of 'characteristic' facies, mental retardation, and the supravalvar lesion. The facies consisted of protruding lips, low set ears, epicanthic folds, and strabismus.

Angiocardiography was performed more regularly in later series of what became known as the supravalvar aortic stenosis syndrome. In all the 10 cases of Beuren *et al.* (1964) there were also peripheral pulmonary arterial stenoses and they suggested that the full syndrome should include this anomaly, as well as a 'metallic' timbre of the voice, dental hypoplasia, and the peripheral systemic arterial stenoses which other workers, at the same time, had been demonstrating angiographically (Beuren, Apitz, and Harmjanz, 1962; Bourassa and Campeau, 1963; Williamson, 1964).

Recognized earlier, but documented contemporaneously with this syndrome and its stigmata, was a familial form of the disease, with which the sufferers had normal facies and mental development, but a strong family history of similar lesion above the aortic valve (Logan *et al.*, 1965). This syndrome became regarded as a separate entity and included sporadic cases without a family history. An interesting series was that of Eisenberg *et al.* (1964), in which 3 generations of 2 families were examined, involving over 100 members. Five proven cases

Received 8 January 1973.

were recorded and a further 8 suspected clinically of having the lesion. None had any of the physical stigmata.

In 1951, Butler had described a case of severe infantile hypercalcaemia associated with abnormal facies in whom there was a cardiac murmur. Fanconi *et al.* (1952) confirmed this 'elfin' facies syndrome and documented it more fully. Other features common to both case reports were a low birthweight, delayed appearance of ossification centres, dense metaphyses, and azotaemia. Further studies revealed a mortality of 25 per cent by 3½ years, usually from renal failure, with nephrocalcinosis a not uncommon feature (Hoevels and Stephan, 1962; Jue, Noren, and Anderson, 1965). The cause of the cardiac murmur was not explained.

Black and Bonham Carter (1963) related the two diseases by pointing out that the 'elfin' facies of Schlesinger was similar to the 'characteristic' facies of Williams. From the 5 cases that they added, in all of whom the supravalvar aortic stenosis was suggested on clinical grounds only, they elicited a history of failure to thrive in infancy. This, they intimated, represented the hypercalcaemic episode and the abnormalities were consequent upon it. Further support associating the syndromes came from Hooft, Vermassen, and Blancquaert (1963) and in 1964, Garcia *et al.* reported the first case of the full supravalvar aortic stenosis syndrome with a documented episode of infantile hypercalcaemia.

### Case histories

**Case 1** A boy was born in 1956 at 36 weeks by caesarian section, performed because of foetal distress. The birthweight was 2038 g and there was no history of

a maternal intake of vitamin D supplements during pregnancy, nor of hypercalcaemia. There was no family history of congenital heart disease.

From the age of 3 to 9 months he failed to thrive and at this time the serum calcium was found to be 12.2 mg/100 ml.

He has the elfin facies of hypercalcaemia, obvious mental retardation, though his IQ has not been documented numerically, a 'metallic' voice, and dental hypoplasia. There are also bilateral radio-ulnar synostoses. The blood pressure is 90/70 mmHg in the left arm and 120/80 mmHg in the right arm, and the left-sided pulse deficit is obvious clinically; a sign present in 9 of our 12 cases and first reported by Franch and Oran (1963). The arterial wave form is normal, but there is a grade 2/4 ejection systolic murmur at the left sternal edge, conducted up into the neck. There is no ejection click, no early diastolic murmur, and the second sound moves normally. The physical signs are consistent with a diagnosis of supravalvar aortic stenosis. The chest x-ray shows a small ascending aorta and knuckle, but is otherwise normal.

At the age of 7 a left renal staghorn calculus was noted on a plain film, and he underwent nephrectomy at the age of 15 because of repeated urinary infections. His urine is now sterile and, as his left ventricular outflow tract obstruction remains mild, catheterization is not considered justifiable.

**Case 2** This boy was born in 1958 at 38 weeks, with a normal birthweight. The pregnancy was normal and there was no relevant maternal or family history. At birth he was noted to have an 'odd' face and a cardiac murmur and was thought to have Down's syndrome.

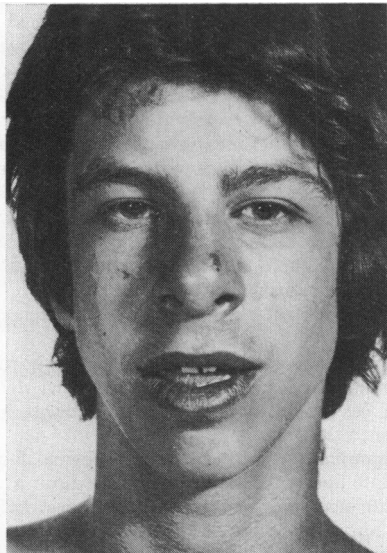


FIG. 1 Case 2: atypical facies of the syndrome, but abnormal.

At the age of 6 weeks he was investigated for failure to thrive, but no serum calcium estimation was obtained and there is no clinical description available to classify it definitely as idiopathic hypercalcaemia in infancy.

On examination now, he does not have Down's syndrome and his chromosome pattern is normal. His facies is abnormal, but not the classical elfin type, though it has some features in common with it (Fig. 1). He has the physical signs of supravalvar aortic stenosis which is not causing significant outflow tract obstruction. The chest x-ray shows a small aortic knuckle and ascending aorta. His renal tract is normal.

**Case 3** This boy was born in 1943 with a normal birthweight and after a normal pregnancy. There was no family history of congenital heart disease, and no failure to thrive suggestive of infantile hypercalcaemia. No relevant maternal history could be elicited. He first presented with a murmur at the age of 5, when his facies and IQ were normal; and at the age of 7, the diagnosis of supravalvar stenosis was confirmed by catheterization and angiocardiology (Fig. 2 and 3).

In addition, there was hypoplasia of the aortic arch, enlargement of both coronary arteries, and mild right innominate artery stenosis. Despite prophylaxis, he developed bacterial endocarditis after the investigations and he suffered a further attack at the age of 19.

Further catheterization showed considerable outflow tract obstruction, with a gradient of 125 mmHg across the stenosis, for which he was operated on with insertion of a Dacron gusset. Seven years later he is well and has a daughter.

**Case 4** The daughter of Case 3 was born in 1968; she is asymptomatic with normal facies and apparently nor-

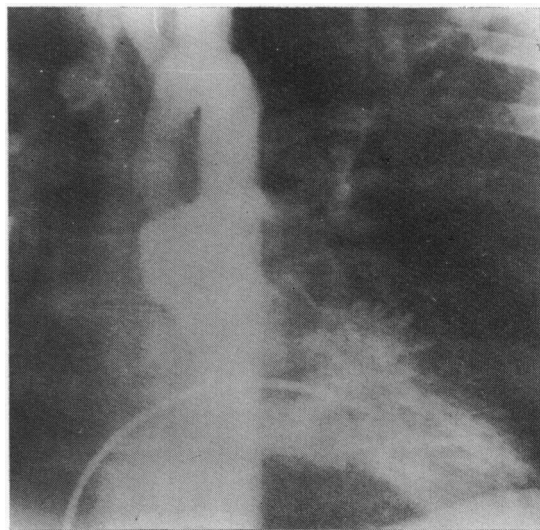


FIG. 2 Case 3: anteroposterior angiogram showing supravalvar aortic stenosis and typical large coronary arteries arising below the stenosis.

mal intelligence, but a murmur was noted at birth. Her mother took no vitamin D supplements during the pregnancy and there is no relevant maternal history. She now has the physical signs of supralvalvar aortic stenosis with a normal carotid pulse, but a grade 3/4 ejection systolic murmur, best heard at the left sternal edge and associated with a thrill going up into the neck. There is no ejection click and only minor electrocardiographic abnormalities. She has not been catheterized as the out-flow tract obstruction remains mild.

**Case 5** This girl was born in 1950, one week *post mature*, with a normal birthweight. She has 9 cousins, 4 with congenital heart disease (Fig. 4). There is no relevant maternal history. Her face is normal and she has an above average intelligence. A murmur was first heard at the age of 10 months, and she was catheterized aged 11 years when the diagnosis of supralvalvar stenosis was confirmed and a 45 mm gradient found across the obstruction. Left ventricular angiocardiography showed only the supralvalvar stenosis, and no arterial stenoses in the branches of the aortic arch. At the age of 17 she developed bacterial endocarditis, but since treatment has been well.

**Case 6** A boy, a cousin of Case 5, was born in 1960, with a normal birthweight and no relevant maternal history. He has normal facies, a normal IQ, and a normal

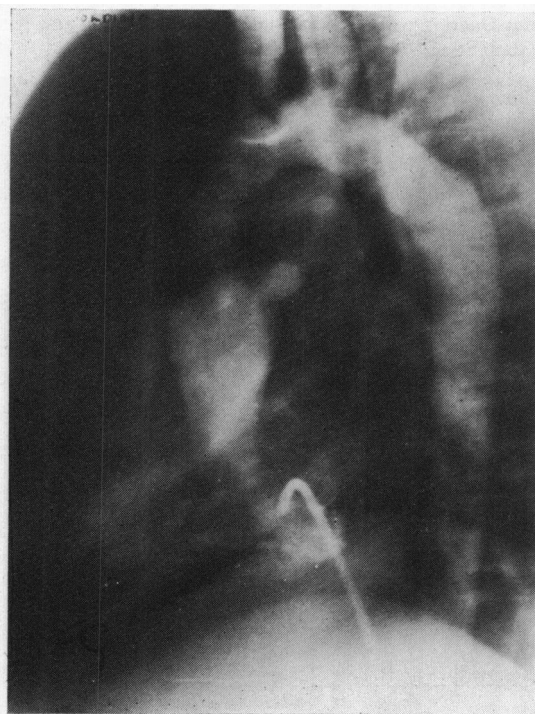


FIG. 3 Case 3: left ventricular angiogram confirming the findings in Fig. 2.

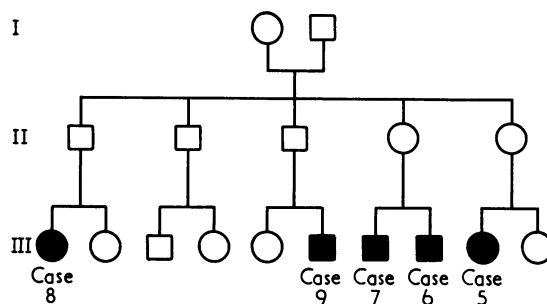


FIG. 4 Family tree of Cases 5 to 9. Affected members are indicated by solid symbols.

renal tract. A murmur was first heard at birth and there is now a grade 3/4 ejection systolic murmur, best heard at the left sternal edge and conducted into the neck. There is no ejection click. The pulse in the left arm is diminished, but the wave form is normal. His electrocardiogram shows no left ventricular hypertrophy, and his chest x-ray shows only a small aortic knuckle and ascending aorta. In view of the mildness of his outflow tract obstruction he has not been investigated.

**Case 7** The brother of Case 6 and a cousin of Case 5, was born in 1958 with a normal birthweight and no relevant maternal history. He has the same physical signs as his brother, including the left brachial pulse defect, and his chest x-ray is similar.

**Case 8** A cousin of Cases 5, 6, 7, and 9, was born in 1971 with a normal birthweight after a normal delivery. There is no relevant maternal history. A murmur was first heard at birth and her face and IQ appear normal.

On examination now there is a diminished pulse in the left arm. The carotid pulse is normal in wave form. A grade 2/4 ejection systolic murmur is heard at the left sternal edge and conducted up into the neck. There is no ejection click and no early diastolic murmur.

The electrocardiogram shows right ventricular hypertrophy and the chest x-ray a large pulmonary artery and a small aortic knuckle.

At catheterization there was a 20 mm gradient across a supralvalvar pulmonary artery stenosis, and angiocardiography confirmed this and showed a stenosis of the right main pulmonary artery in addition.

A coincidental left-sided lesion has not been excluded.

**Case 9** Another cousin of Cases 5–8 was born in 1961 with a normal birthweight after a normal delivery. A murmur was first heard at birth and there was no episode of failure to thrive.

On examination now, he has a normal face and a normal intelligence. There is a slightly diminished pulse in the left arm to palpation and there are the physical signs of supralvalvar aortic stenosis. The electrocardiogram is normal and the chest x-ray shows only the characteristic small aorta of this condition, present in 7 of our 12 cases and previously described in 38 per cent of the cases of Kurlander *et al.* (1966).

**Case 10** Born in 1949 after a normal delivery, with a birthweight of 2490 g, her mother had taken no vitamin D supplements during the pregnancy and there was no family history of congenital heart disease. She appeared normal at birth but, at the age of 6 months, failed to thrive and was admitted to hospital with persistent vomiting. No abnormality was found, and the serum calcium was not measured. Improvement was slow and it was not until the age of 10 years that she began to grow normally. It was about this time that her abnormal facies and cardiac murmur were first noted, but reviewing old photographs, her face had been abnormal since infancy.

On examination now she is 137 cm tall, has typical elfin facies (Fig. 5), a 'metallic' voice, dental hypoplasia with carious teeth, and obvious mental retardation. Her IQ was measured as 47 (Termann Merrill) aged 7, but it appears higher than that now. There is a diminished pulse in the left arm, but the arterial wave form is normal. The physical signs are those of supravalvar aortic stenosis. The electrocardiogram shows no left ventricular hypertrophy, but the ST segments are abnormal. The chest x-ray shows a small aortic knuckle and several peripheral pulmonary arterial stenoses are suspected on the plain film. These are not visible on the illustration (Fig. 6) and have not been confirmed angiographically because she does not merit catheterization. A similar chest x-ray has been described previously by Kurlander *et al.* (1966).

Her bone age is normal and there is no renal calcification.

**Case 11** Born in 1949 with a normal birthweight after a normal pregnancy, there was no relevant maternal

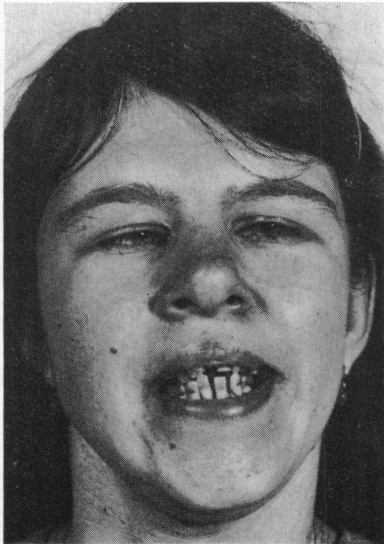


FIG. 5 Case 10: typical facies of supravalvar aortic stenosis syndrome.

history and no family history of congenital heart disease. She has normal facies and a normal intelligence.

She presented at the age of 13 years with progressive dyspnoea. At catheterization she was found to have supravalvar aortic stenosis with a gradient of 75 mm. A mild innominate artery stenosis was seen on the angiogram and both coronary arteries were characteristically large. She was operated upon with insertion of a Teflon gusset and since then has been well and asymptomatic.

She now has a daughter who is normal and has no cardiac murmur.

**Case 12** Born in 1961 at 33½ weeks with a birthweight of 2265 g, after otherwise normal pregnancy; his mother had taken no vitamin D supplements during it and there was no family history of congenital heart disease.

A murmur was first heard at the age of 6 months, when he thrived poorly for 3 months and failed to gain weight. However, no serum calcium estimation was performed. After this episode, he always remained below the third centile.

By the age of 10 he had considerable exertional dyspnoea and on examination then had the characteristic facies of the idiopathic hypercalcaemia of infancy syndrome, despite previous surgery for strabismus and abnormal ears. He is subnormal and attends a special school. No abnormality can be demonstrated in his renal tract.

The physical signs suggested moderate left ventricular outflow tract obstruction and the electrocardiogram

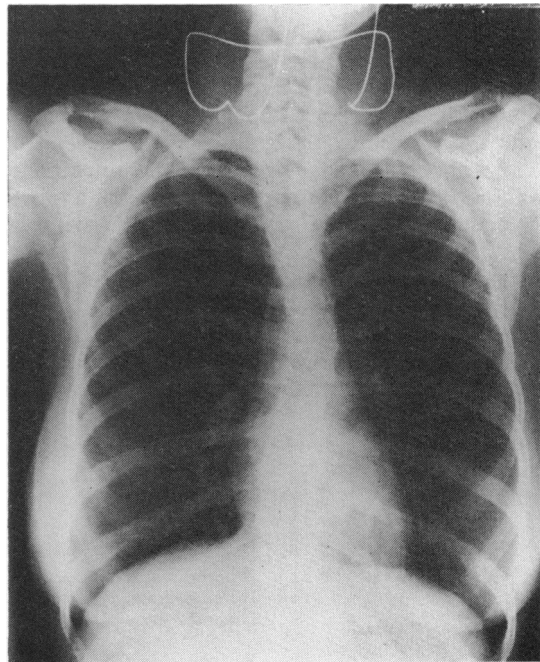


FIG. 6 Case 10: chest x-ray showing small aortic knuckle.

showed some left ventricular hypertrophy. The chest x-ray was normal apart from a small aorta.

The diagnosis of supralvalvar aortic stenosis was confirmed at angiocardiography, and distal to the stenosis the ascending aorta was hypoplastic. Both coronary arteries were characteristically large. Right heart catheterization showed a pulmonary artery pressure of 50/20 mmHg suggestive of peripheral pulmonary artery stenoses.

Surgery was undertaken in 1971 with excision of the stenosis and insertion of a Teflon patch. Since then he has been well and asymptomatic.

### Analysis of clinical features

A review of the English language published reports reveals 200 cases of supralvalvar aortic stenosis, and these are indicated on a separate list headed 'further bibliography' if not otherwise referred to in the paper. Their various clinical features are considered below and our 12 cases included (Table).

(a) **Presence of physical stigmata** Eighty-nine cases had abnormal facies which were either the classical elfin type, or intermediate forms as in our Case 2. Such a range of physical abnormalities was first described by Antia *et al.* (1967). They may or may not have impairment of intellect and not all give a history of failure to thrive in infancy.

(b) **Family history** No case with physical stigmata has a positive family history, though 4 patients have a sib with mental retardation. However, no details of their facies or cardiac status are available. Among the 123 cases without stigmata, a positive family history is available in only 51. Several of those without such a history may be first mutations, as in our Case 3, but there must exist too, a group of sporadic idiopathic supralvalvar aortic stenosis.

The aetiology of some of these will be discussed later.

(c) **Direct evidence of hypercalcaemia** Only 7 patients had documented evidence of hypercalcaemia in infancy and all had obvious physical stigmata. It is therefore an infrequent pointer to the diagnosis and even a history of failure to thrive in infancy may be absent.

(d) **Lesions of renal tract** Three of the 89 patients with facial abnormalities had nephrocalcinosis visible on the plain x-ray (Antia *et al.*, 1967; Black, Butler, and Schlesinger, 1965), one of whom also had a calculus (Jue *et al.*, 1965). Two further patients had calculi without nephrocalcinosis (Vysloulzil, Endrys, and Steinhart, 1964) (Case 1).

One patient, with normal facies and intelligence, had bilateral calculi, and Myers and Willis (1966) suggested that there must have been an infantile hypercalcaemic episode, but gave no indication of it in the clinical history. Certainly, there was no family history of an aortic lesion. This is the only case of calculus nephropathy among the so-called familial cases.

(e) **Presence of multiple vascular lesions** Of 175 patients investigated adequately, peripheral arterial stenoses were reported in about 60 per cent, but in almost every case the examination was limited to the aortic arch and/or pulmonary trunk and did not include more distal arteries. The incidence may therefore be higher. Little significant difference exists in the incidence between those with facial abnormalities and those without.

TABLE *Clinical features of 12 Cases*

Case No.	Physical stigmata	Family history	Other vascular lesions	Brachial pulse deficit	Chest x-ray
1	+	o	No angiogram	Left	Small aorta
2	+	o	No angiogram	Right	Small aorta
3	o	+	Peripheral systemic arterial stenoses	Right	Normal
4	o	+	No angiogram	None	Normal
5	o	+	None	Right	Normal
6	o	+	No angiogram	Left	Small aorta
7	o	+	No angiogram	Left	Small aorta
8	o	+	Supralvalvar pulmonary artery stenosis; peripheral pulmonary artery stenosis	Left	Small aorta
9	o	+	No angiogram	Left	Small aorta
10	+	o	No angiogram	Left	Small aorta; peripheral pulmonary artery stenoses
11	o	o	Peripheral systemic arterial stenosis	None	Normal
12	+	o	Peripheral pulmonary artery stenoses; hypoplasia of aorta	None	Normal

## Discussion

The relation of the supravalvar aortic stenosis syndrome to idiopathic hypercalcaemia of infancy has been clarified. Presentation is either soon after birth in the acute hypercalcaemic episode or in the late normocalcaemic stage. The acute group are diagnosed as idiopathic hypercalcaemia of infancy, regardless of their cardiac lesion, which at that stage is usually of only secondary importance. In the late normocalcaemic stage, the diagnosis depends on the cardiac status. Those with supravalvar aortic stenosis form the supravalvar aortic stenosis syndrome, while those without form the late normocalcaemic stage of the idiopathic hypercalcaemia of infancy syndrome (Fraser *et al.*, 1966).

Few cases have been investigated cardiologically during the acute hypercalcaemic episode, but Wiltse *et al.* (1966) described identical twins who had only peripheral pulmonary arterial stenoses. Fraser *et al.* (1966) found the same lesion in another patient in the acute stage. Eie *et al.* (1972) found peripheral pulmonary arterial stenoses associated with coarctation in another patient with the acute syndrome. In Rashkind, Golinko, and Arcasoy's original series (1961), which included 11 necropsy cases of idiopathic hypercalcaemia of infancy, none had supravalvar aortic stenosis but 7 had cardiac abnormalities. Black *et al.* (1965) did report one case, however, of idiopathic hypercalcaemia of infancy in whom at necropsy there was supravalvar aortic stenosis, but the range of cardiovascular abnormalities in idiopathic hypercalcaemia of infancy is obviously large, and while it has been convenient to separate the late normocalcaemic stage into those with supravalvar aortic stenosis and those without it is obviously artificial. Those cases with only peripheral pulmonary arterial stenosis and all the physical stigmata are equally a part of the syndrome, and may be included in it by designating all as the late normocalcaemic stage of the idiopathic hypercalcaemia of infancy syndrome.

**Aetiology** A study of 212 cases with the late normocalcaemic idiopathic hypercalcaemia of infancy syndrome reveals 8 patients (including our Case 2) in whom the facies were abnormal at birth. Prenatal factors are therefore implicated and it seems more likely that the hypercalcaemia is a manifestation of the same complex of metabolic abnormalities, which results in the characteristic vascular, facial, and other findings.

Many more cases of idiopathic hypercalcaemia of infancy were described in England where it was routine for pregnant women to be given vitamin D supplements than in countries where this was not

the practice, and moreover, the incidence fell when these supplements were reduced by half.

Beuren (1965) reported 2 cases given massive doses of vitamin D in error, both of whom developed supravalvar aortic stenosis and became mentally retarded. Animal experiments by Friedman and Roberts (1966) demonstrated aortic abnormalities in 40 per cent of the progeny of rabbits given large amounts of the vitamin during pregnancy, and in 24 per cent, these resembled the human lesion; 70 per cent of them had craniofacial abnormalities.

Although supravalvar aortic stenosis and hypercalcaemia can be related to excessive intake of vitamin D, there is no evidence in most cases, including ours, that either the mothers, or the infants, have had an excessive intake. It has been suggested (Antia, 1965) that patients with the syndrome handle vitamin D differently from normals, and Fellers and Schwartz (1958) have described it as an inborn error of metabolism, a characteristic of which is deranged foetal handling of vitamin D. Forfar wonders whether or not there may be a toxic metabolite produced in the mother or the foetus from the abnormal handling and breakdown of the vitamin (Forfar *et al.*, 1956).

Whatever the metabolic defect, it may express itself in several ways: (a) by the production of an episode of hypercalcaemia frequently severe enough to result in renal damage; (b) by the production of vascular lesions, of which supravalvar aortic stenosis is commonly the most significant clinically; and (c) by mental deficiency, craniofacial dysplasia, and the other common features, of which some may result from the original insult, e.g. intellectual impairment, others may be a direct consequence of the other abnormalities, e.g. pyloric stenosis as a manifestation of hypercalcaemia, while others may be less specific manifestations of general ill health during infancy, e.g. delayed skeletal maturation.

The degree to which each expression proceeds may be independently variable; a number of patients with hypercalcaemia will also develop supravalvar stenosis and vice versa, and the associated stigmata will be present to an extent not necessarily related to either. Some patients may therefore show pure supravalvar aortic stenosis without any of the other components of the syndrome, and others, peripheral pulmonary arterial stenosis rather than systemic arterial lesions.

Possible causes for this metabolic defect, or inborn error of metabolism, logically include only three factors: (a) environmental, (b) chromosomal, and (c) a single gene mutation. Environmental factors can be excluded, as no patient has been shown to have an intake of vitamin D which would be excessive in the normal, though sensitization to normal

amounts has been considered above. Chromosomal studies by Merritt *et al.* (1963) have shown no detectable abnormality. A single gene mutation therefore seems the most likely.

This could have two main pathways. Firstly, to cause a metabolic defect in vitamin D handling, as detailed above, perhaps by a single enzyme defect; or secondly, to produce supra-avalvar stenosis and other vascular stenoses as a genetic defect. Both of these factors could be transmitted with varying penetrance to exhibit either as the idiopathic hypercalcaemia of infancy syndrome, or as the spontaneous or familial form of supra-avalvar aortic stenosis. Each may be potentially inheritable, though inheritance has only been documented in the so-called familial type.

The late normocalcaemic stage of the idiopathic hypercalcaemia in infancy syndrome will therefore contain patients with supra-avalvar aortic stenosis and the physical stigmata, patients without supra-avalvar aortic stenosis but possessing physical stigmata, and some patients with supra-avalvar aortic stenosis and minimal or no stigmata. Equally, patients with normal facies, birthweight, and intelligence, whether or not they have a positive family history, may represent the familial form, the sporadic idiopathic group, or even, rarely, the late normocalcaemic stage of the idiopathic hypercalcaemia of infancy syndrome. Under these circumstances, rigid differentiation into the supra-avalvar aortic syndrome and the familial form may serve only to confuse. Once the aetiology is documented and the enzyme defect isolated, if indeed it is the cause, it will be once more possible to classify these patients adequately.

We are grateful to Dr. N. A. J. Hamer for his advice and encouragement and for permission to study his patients; and to Dr. G. W. Hayward and Mr. O. S. Tubbs; also to Drs. Stone and Radley Smith for information about three of these patients. We are also grateful to the Department of Medical Illustration of St. Bartholomew's Hospital.

## References

- Antia, A. U. (1965). Personal communication to Taussig (1967).
- Antia, A. U., Wiltse, H. E., Rowe, R. D., Pitt, E. L., Levin, S., Ortesen, O. E., and Cooke, R. E. (1967). Pathogenesis of the supra-avalvar aortic stenosis syndrome. *Journal of Pediatrics*, **71**, 431.
- Beuren, A. J. (1965). Personal communication to Taussig (1967).
- Beuren, A. J., Apitz, J., and Harmjanz, D. (1962). Supra-avalvar aortic stenosis in association with mental retardation and a certain facial appearance. *Circulation*, **26**, 1235.
- Beuren, A. J., Schultze, C., Eberle, P., Harmjanz, D., and Apitz, J. (1964). The syndrome of supra-avalvar aortic stenosis, peripheral pulmonary stenosis, mental retardation and similar facial appearance. *American Journal of Cardiology*, **13**, 471.
- Black, J. A., and Bonham Carter, R. E. (1963). Association between aortic stenosis and facies of severe infantile hypercalcaemia. *Lancet*, **2**, 745.
- Black, J. A., Butler, N. R., and Schlesinger, B. E. (1965). Aortic stenosis and hypercalcaemia. *Lancet*, **2**, 546.
- Bourassa, M. G., and Campeau, L. (1963). Combined supra-avalvar aortic and pulmonic stenosis. *Circulation*, **28**, 572.
- Butler, N. R. (1951). Generalized retardation, with renal impairment, hypercalcaemia, and osteosclerosis of skull. *Proceedings of the Royal Society of Medicine*, **44**, 296.
- Denie, J. J., and Verheugt, A. P. (1958). Supra-avalvar aortic stenosis. *Circulation*, **18**, 902.
- Eie, H., Semb, G., Muller, O., and Bramness, G. (1972). Localised supra-avalvar aortic stenosis combined with mental retardation and peculiar facial appearance. *Acta Medica Scandinavica*, **191**, 517.
- Eisenberg, R., Young, D., Jacobson, B., and Boito, A. (1964). Familial supra-avalvar aortic stenosis. *American Journal of Diseases of Children*, **108**, 341.
- Fanconi, G., Girardet, P., Schlesinger, B. E., Butler, N. R., and Black, J. A. (1952). Chronische Hypercalcaemie, kombiniert mit Osteosklerose, Hyperazotämie, Minderwuchs und kongenitalen Missbildungen. *Helvetica Paediatrica Acta*, **7**, 314.
- Fellers, F. X., and Schwartz, R. (1958). Aetiology of the severe form of idiopathic hypercalcaemia of infancy, a defect in vitamin D metabolism. *New England Journal of Medicine*, **259**, 1050.
- Forfar, J. O., Balf, C. L., Maxwell, G. M., and Thompsett, S. L. (1956). Idiopathic hypercalcaemia of infancy, clinical and metabolic studies with special reference to the aetiological role of vitamin D. *Lancet*, **1**, 981.
- Franch, R. H., and Oran, E. (1963). Asymmetric arm and neck pulses. A clue to supra-avalvar aortic stenosis (abstract). *Circulation*, **28**, 722.
- Fraser, D., Kidd, B. S. L., Kooh, S. W., and Paunier, L. (1966). A new look at infantile hypercalcaemia. *Pediatric Clinics of North America*, **13**, 503.
- Friedman, W. F., and Roberts, W. C. (1966). Vitamin D and the supra-avalvar aortic stenosis syndrome. *Circulation*, **34**, 77.
- Garcia, R. E., Friedman, W. F., Kaback, M. M., and Rowe, R. D. (1964). Idiopathic hypercalcaemia and supra-avalvar aortic stenosis. Documentation of a new syndrome. *New England Journal of Medicine*, **271**, 117.
- Hoevens, O., and Stephan, U. (1962). Das Krankheitsbild der 'idiopathischen' Hypercalcaemie eine chronische Vitamin D Intoxikation. *Ergebnisse der inneren Medizin und Kinderheilkunde*, **18**, 116.
- Hoof, C., Vermassen, A., and Blancquaert, A. (1963). Observations concerning the evolution of the chronic form of idiopathic hypercalcaemia in children. *Helvetica Paediatrica Acta*, **18**, 138.
- Jue, K. L., Noren, G. R., and Anderson, R. C. (1965). The syndrome of idiopathic hypercalcaemia of infancy with associated congenital heart disease. *Journal of Pediatrics*, **67**, 1130.
- Kurlander, G. J., Petry, E. L., Taybi, H., Lurie, P. R., and Campbell, J. A. (1966). Supra-avalvar aortic stenosis. *American Journal of Roentgenology*, **98**, 782.
- Logan, W. F. W. E., Wyn Jones, E., Walker, E., Coulshed, N., and Epstein, E. J. (1965). Familial supra-avalvar aortic stenosis. *British Heart Journal*, **27**, 547.
- Merritt, A. D., Palmer, C. G., Lurie, P. R., and Petry, E. L. (1963). Supra-avalvar aortic stenosis. Genetic and clinical studies (abstract). *Journal of Laboratory and Clinical Medicine*, **62**, 995.



- Myers, A. R., and Willis, P. W. (1966). Clinical spectrum of supravalvular aortic stenosis. *Archives of Internal Medicine*, **118**, 552.
- Rashkind, W. J., Golinko, R., and Arcasoy, M. (1961). Cardiac findings in idiopathic hypercalcaemia of infancy. *Journal of Pediatrics*, **58**, 464.
- Vysloulzil, J., Endrys, J., and Steinhart, L. (1964). Congenital supravalvular aortic stenosis with mitral insufficiency. *Cor et Vasa*, **6**, 164.
- Williams, J. C. P., Barratt-Boyes, B. G., and Lowe, J. B. (1961). Supravalvular aortic stenosis. *Circulation*, **24**, 1311.
- Williamson, D. A. J. (1964). Supravalvular aortic stenosis associated with mental and physical retardation and a characteristic facies. *Proceedings of the Royal Society of Medicine*, **57**, 118.
- Wiltse, H. E., Goldbloom, R. B., Antia, A. U., Ottesen, O. E., Rowe, R. D., and Cooke, R. E. (1966). Idiopathic hypercalcaemia syndrome in twins. *New England Journal of Medicine*, **275**, 1157.
- Further bibliography**
- Becker, A. E., Becker, M. J., and Edwards, J. E. (1972). Mitral valvular abnormalities associated with supravalvular aortic stenosis. *American Journal of Cardiology*, **29**, 90.
- Burby, A. F. (1958). Supra-aortic stenosis associated with Marfan's syndrome. *British Heart Journal*, **20**, 143.
- Chantler, C., Hywel Davies, E., and Joseph, M. C. (1966). Cardiovascular and other associations of infantile hypercalcaemia. *Guy's Hospital Reports*, **115**, 221.
- Cheu, S., Fiese, M. J., and Hatayama, E. (1957). Supra-aortic stenosis; congenital, supra-aortic valvular, stenosing membrane on the aortic cusps. *American Journal of Clinical Pathology*, **28**, 293.
- De Baakey, M. E., and Beall, A. C. (1963). Successful surgical correction of supravalvular aortic stenosis. *Circulation*, **27**, 858.
- Dotter, C. T., Bristow, J. D., Menashe, V. D., Starr, A., and Griswold, H. E. (1961). Stenosis of left ventricular outflow tract. *Circulation*, **23**, 823.
- Dupont, B., Dupont, A., Bliddal, J., Holst, E., Melchior, J. C., and Ottesen, O. E. (1970). Idiopathic hypercalcaemia of infancy. *Danish Medical Bulletin*, **17**, 33.
- Farrehi, C., Dotter, C. T., and Griswold, H. E. (1964). Supravalvular aortic stenosis; underdevelopment and characteristic facies. *American Journal of Diseases of Children*, **108**, 335.
- Fay, J. E., Lynn, R. B., and Partington, M. W. (1966). Supravalvular aortic stenosis, mental retardation and a characteristic facies. *Canadian Medical Association Journal*, **94**, 295.
- Hara, M., Dungan, T., and Lincoln, B. (1962). Supravalvular aortic stenosis. Report of successful excision and aortic reanastomosis. *Journal of Thoracic and Cardiovascular Surgery*, **43**, 212.
- Kahler, R. L., Braunwald, E., Plauth, W. H., and Morrow, A. G. (1966). Familial congenital heart disease. *American Journal of Medicine*, **40**, 384.
- Kostis, J. B., and Moghadam, A. N. (1970). Syndrome of supravalvular aortic stenosis. *Chest*, **57**, 253.
- Kupic, E. A., and Abrams, H. L. (1966). Supravalvular aortic stenosis. *American Journal of Roentgenology*, **98**, 822.
- Lightwood, R. (1952). Idiopathic hypercalcaemia in infants with failure to thrive. In *Proceedings of the British Paediatric Association. Archives of Disease in Childhood*, **27**, 302.
- Lillehei, C. W., Levy, M. J., Varco, R. L., Wang, Y., Adams, P., and Anderson, R. C. (1962). Surgical treatment of congenital aortic stenosis by cardiopulmonary bypass. *Circulation*, **26**, 856.
- McGoon, D. C., Mankin, H. T., Vlad, P., and Kirklin, J. W. (1961). Surgical treatment of supravalvular aortic stenosis. *Journal of Thoracic Surgery*, **41**, 125.
- Morrow, A. G., Waldhausen, J. A., Peters, R. L., Bloodwell, R. D., and Braunwald, E. (1959). Supravalvular aortic stenosis. Clinical, haemodynamic and pathologic observations. *Circulation*, **20**, 1003.
- Page, H. L., Vogel, J. H. K., Pryor, R., and Blount, S. G. (1965). Unusual observations in supravalvular aortic stenosis. *Circulation*, **32**, Suppl. 2, 166.
- Payne, W. W. (1952). The blood chemistry in idiopathic hypercalcaemia. In *Proceedings of the British Paediatric Association. Archives of Disease in Childhood*, **27**, 302.
- Perou, M. L. (1961). Congenital supravalvular aortic stenosis. A morphological study with attempt at classification. *Archives of Pathology*, **71**, 453.
- Peterson, T. A., Todd, D. B., and Edwards, J. E. (1965). Supravalvular aortic stenosis. *Journal of Thoracic and Cardiovascular Surgery*, **50**, 734.
- Priest, J. H., and Lang, D. M. (1965). Aortic stenosis and hypercalcaemia. *Lancet*, **1**, 1335.
- Rastelli, G. C., McGoon, D. C., Ongley, P. A., Mankin, H. T., and Kirklin, J. W. (1966). Surgical treatment of supravalvular aortic stenosis. *Journal of Thoracic and Cardiovascular Surgery*, **51**, 873.
- Sarin, R. K., Ross, A. M., Rose, L. I., Rios, J. C., and Massumi, R. A. (1968). Combined supra-aortic stenosis and pulmonary arterial stenosis. *Angiology*, **19**, 293.
- Scheinin, T. M., Inberg, M. V., and Kallio, V. (1969). Supravalvular aortic stenosis and multiple aneurysms of the ascending aorta. *Scandinavian Journal of Thoracic and Cardiovascular Surgery*, **3**, 107.
- Shumacker, H. B., and Mandelbaum, I. (1965). Surgical considerations in the management of supravalvular aortic stenosis. *Circulation*, **31**, Suppl. 1, 36.
- Starr, A., Dotter, C., and Griswold, H. (1961). Supravalvular aortic stenosis: diagnosis and treatment. *Journal of Thoracic Surgery*, **41**, 134.
- Tami, M. (1967). Supravalvular aortic stenosis. A case report. *Rhode Island Medical Journal*, **50**, 401.
- Taussig, H. B. (1966). Possible injury to the cardiovascular system from vitamin D. *Annals of Internal Medicine*, **65**, 1195.
- Underhill, W. L., Tredway, J. B., D'Angelo, G. J., and Baay, J. E. W. (1971). Familial supravalvular aortic stenosis. *American Journal of Cardiology*, **27**, 560.
- Wooley, C. F., Hosier, D. M., Booth, R. W., Molnar, W., Sirak, H. D., and Ryan, J. M. (1961). Supravalvular aortic stenosis. Clinical experiments with four patients including familial occurrence. *American Journal of Medicine*, **31**, 717.
- Wunsch, C., Feiganbaum, H., Campbell, R., and Helmen, C. (1967). A case of valvular and supravalvular aortic stenosis and coarctation of the aorta. *American Journal of Cardiology*, **19**, 275.

Requests for reprints to Dr. E. C. Martin, Diagnostic Radiology Department, St. Bartholomew's Hospital, London E.C.1.